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MORBO DI PAGET

Simone Parisi

AOU Città della Salute e della Scienza di Torino - SC Reumatologia

Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

Webinar
16-17 ottobre 2020

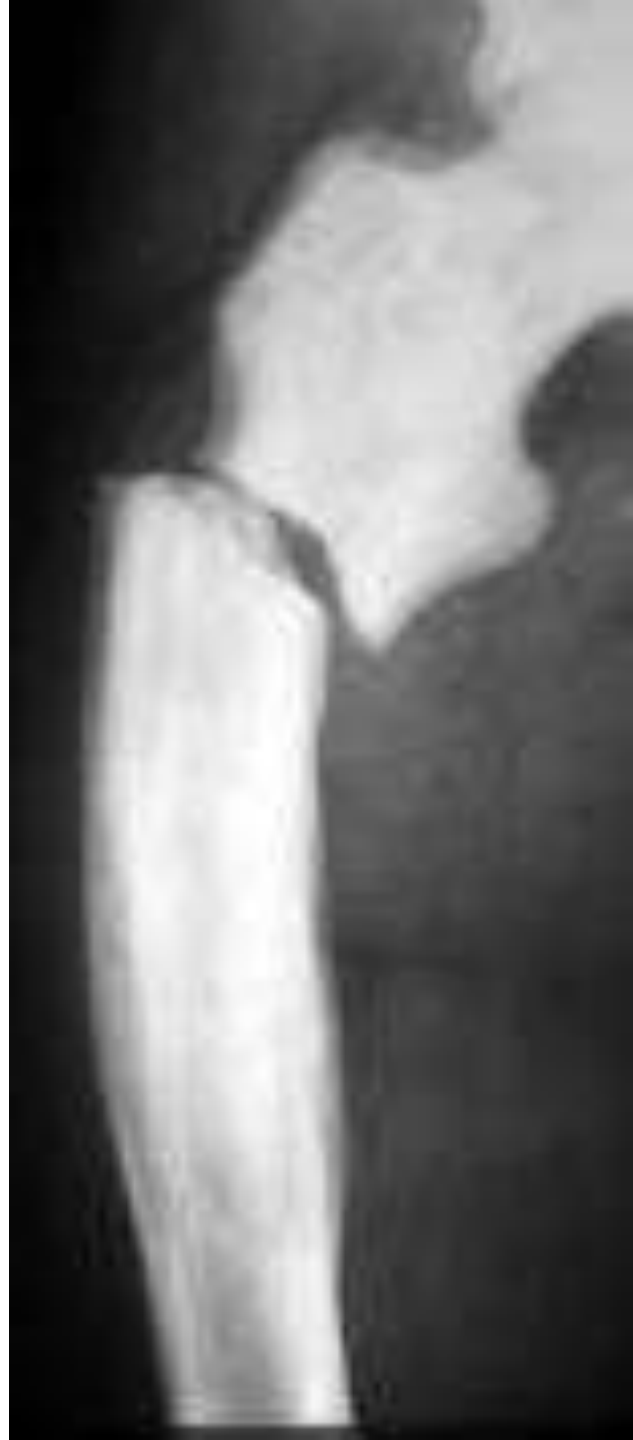
ABBVIE, AMGEN, BALDACCI, BIOGEN, BMS, CELGENE, CHIESI, GRUNENTHAL, JANSSEN, NOVARTIS, PFIZER, LILLY, SANOFI, UCB

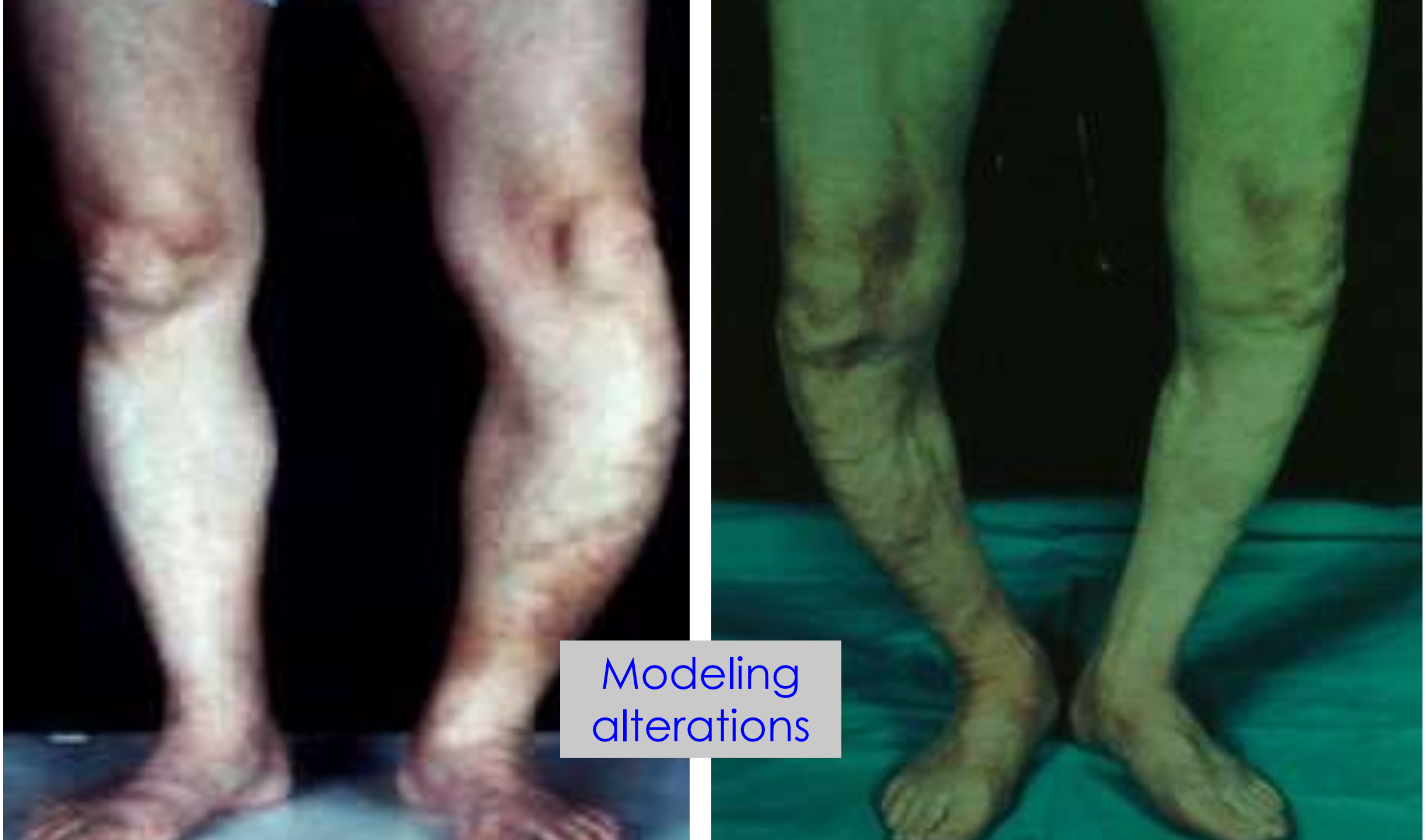
James Paget
1877

Osteitis deformans

Paget's disease of bone

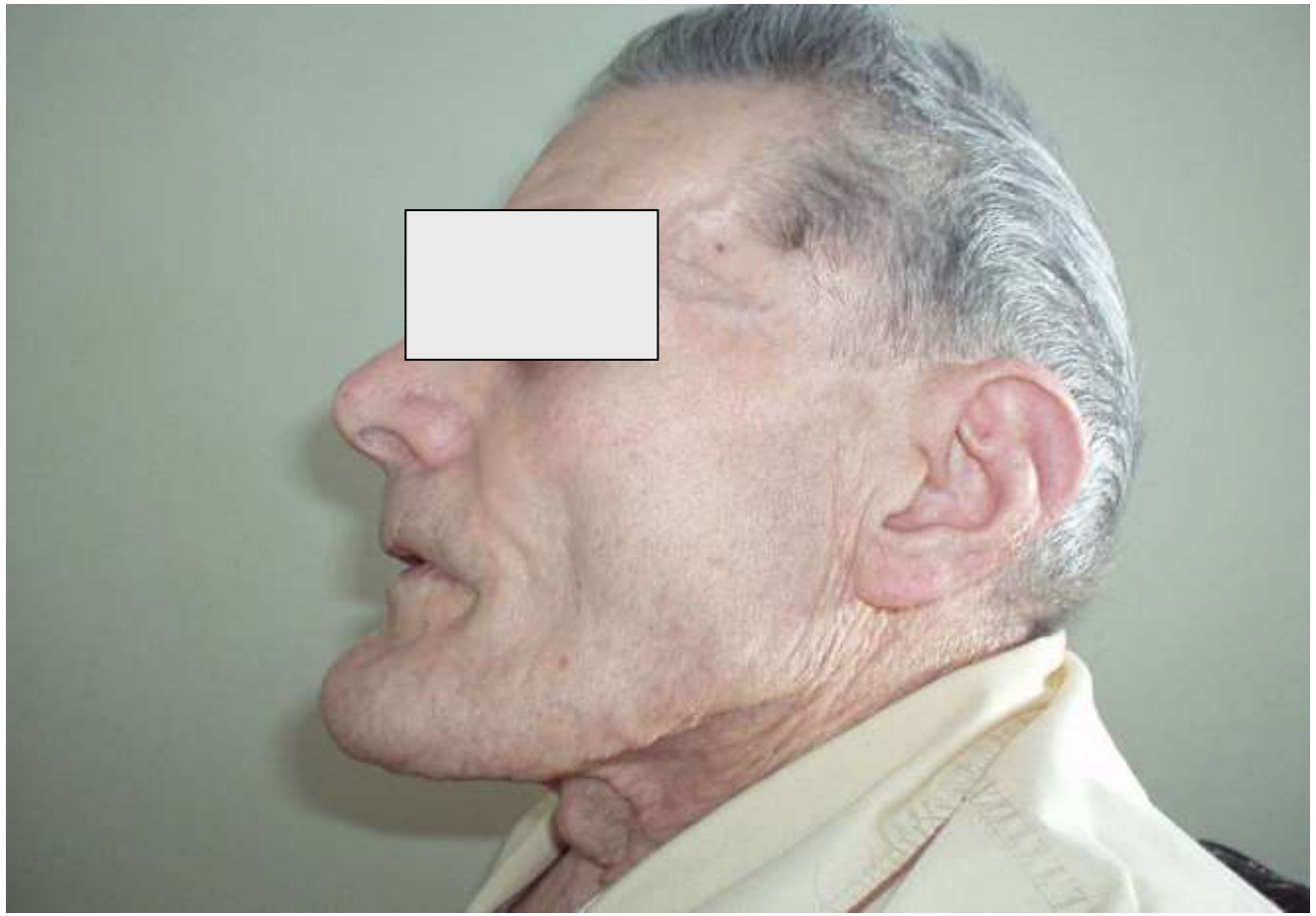
- Disorder of bone remodeling in which there is **excessive bone resorption** followed by **excessive bone formation** that results in bone that is architecturally unsound.
- The excess bone lacks the structural stability of normal bone, causing **deformity**, **pain**, and **fracture** in one or more regions of the skeleton

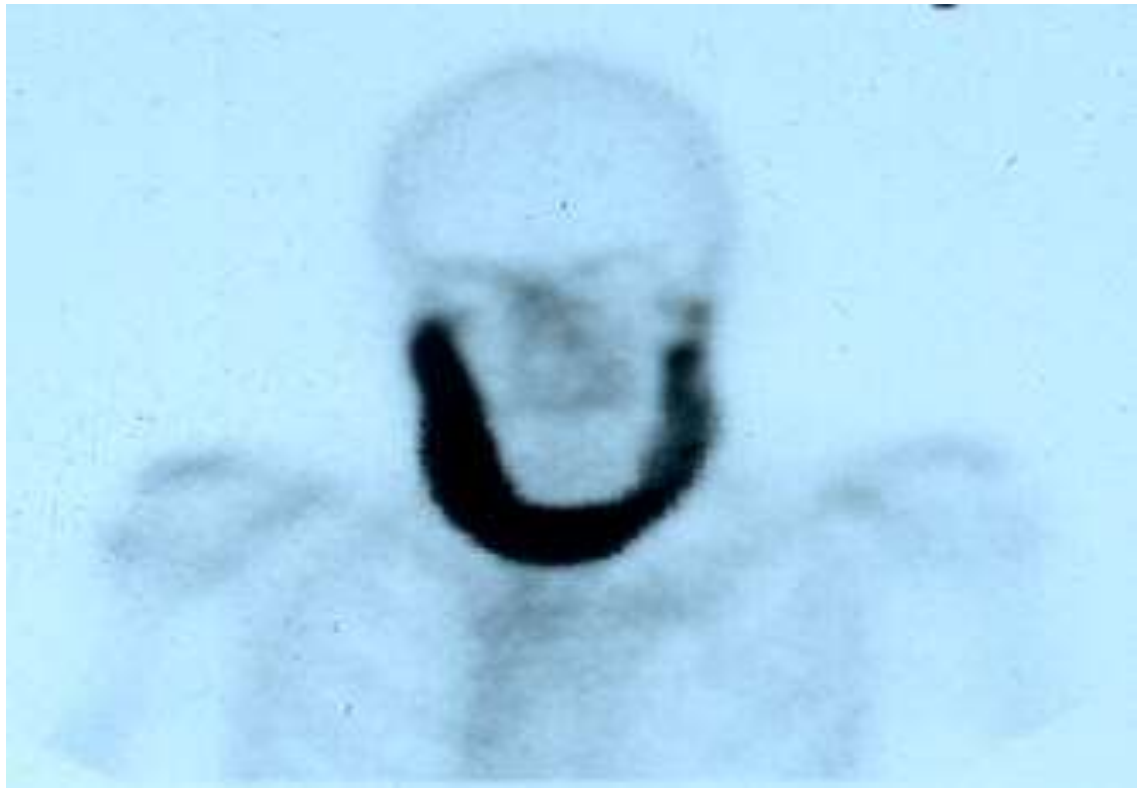



Modeling
alterations

Morbo di Paget

Localizzazioni cranio-facciali





Paget's disease

Table I - Clinical presentation of Paget disease of bone.

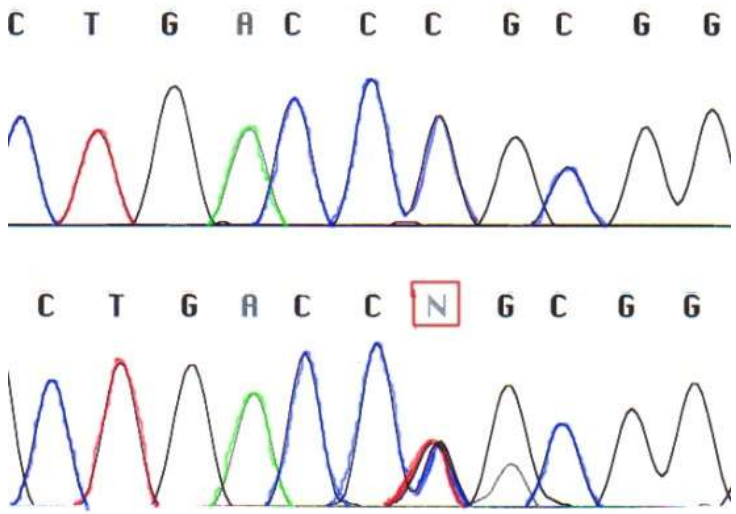
Incidental finding on an x-ray or in biochemical test
Bone pain
Arthopathy
Deformity
Fracture
Hearing loss
Neurological complications
Osteosarcoma

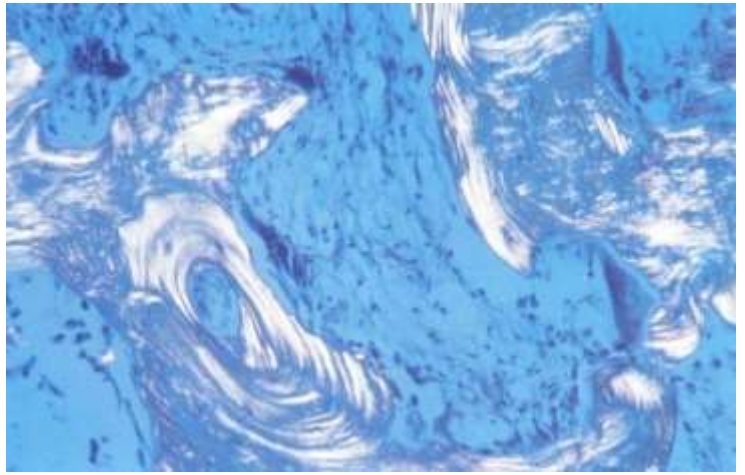
- Diagnosis in the early phase is uncommon
- Often asymptomatic
- Pain attributed to osteoartrhitis
- Serum ALP not correctly evaluated
- In some cases, diagnosis was made after complications are developed

DIAGNOSIS OF PAGET'S DISEASE OF BONE

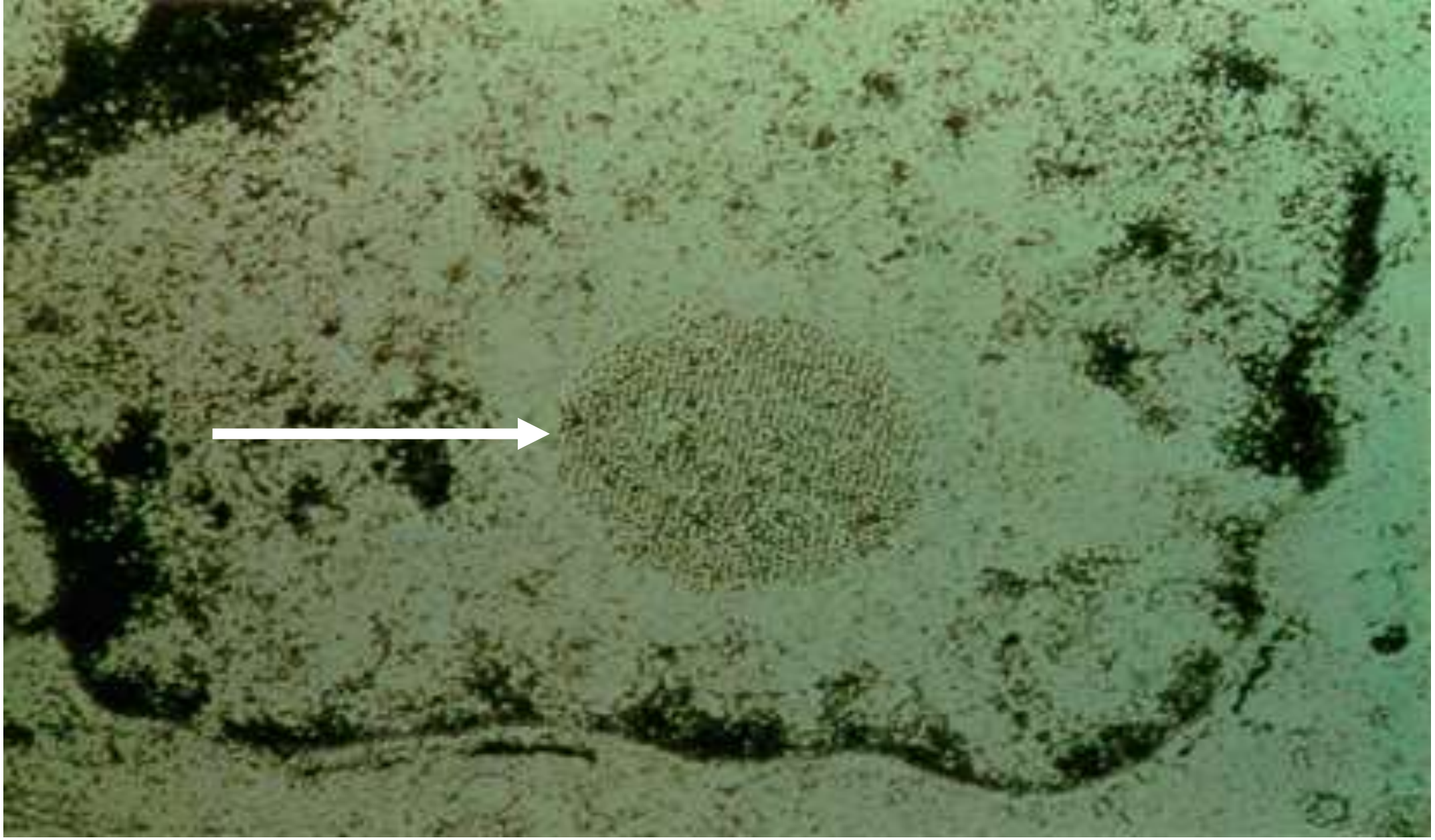
- Signs and Symptoms *(bone deformities)*
- Bone Markers *(high alkaline phosphatase)*
- X-rays
- Bone Scan *(^{99m}Tc-MDP)*
- (CT and/or MRI)

- *SQSTM1* Gene Analysis

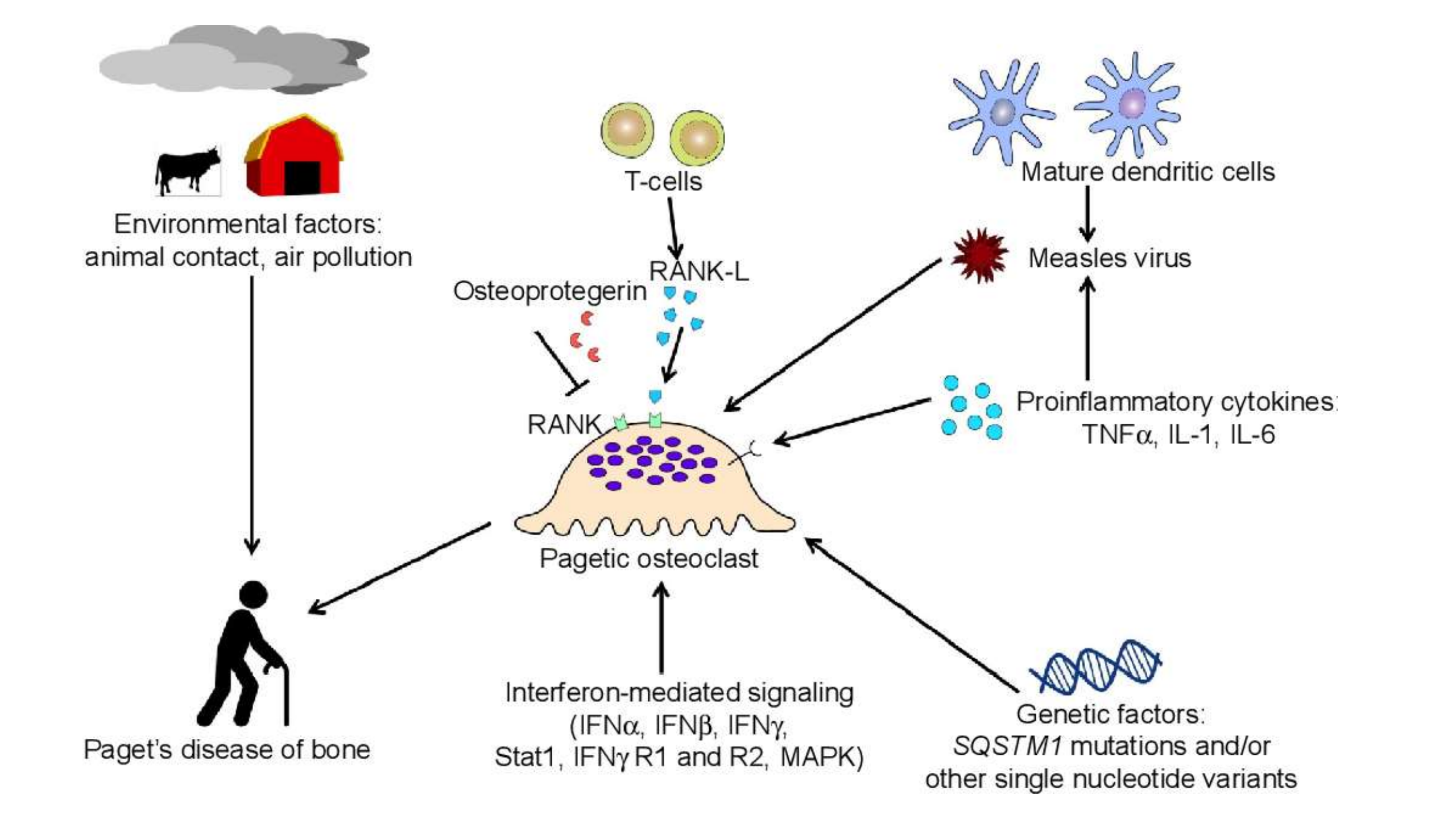




- (Bone Biopsy)



The cause of Paget's disease is still not clear. Research findings suggest that PD may caused by a slow virus infection, possibly related to paramixovirus family


Environmental factors:
animal contact, air pollution
T-cells
RANK-L
Osteoprotegerin
RANK
Mature dendritic cells
Measles virus
Proinflammatory cytokines:
TNFα, IL-1, IL-6
Pagetic osteoclast
Paget's disease of bone
Interferon-mediated signaling
(IFNα, IFNβ, IFNγ,
Stat1, IFNγ R1 and R2, MAPK)
Genetic factors:
SQSTM1 mutations and/or
other single nucleotide variants

EZIOLOGIA

- Familiarità nel 15-30% dei casi.
- Nei parenti di primo grado rischio > 7-10 volte.

→ **IPOTESI GENETICA**

la suscettibilità genetica potrebbe non essere condizione sufficiente

- Penetranza incompleta nelle famiglie con una documentata predisposizione genetica,
- Malattia altamente localizzata a uno o più particolari distretti ossei piuttosto che interessare l'intero scheletro,
- Cambiamenti nell'incidenza e nella severità nel corso degli ultimi 25 anni,
- Maggiore prevalenza della malattia in aree rurali

→ **IPOTESI VIRALE**

Epidemiologia del Morbo di Paget

- Alta prevalenza:
  - Inghilterra, U.S.A., Australia, Nuova Zelanda, Europa Occidentale
- Bassa prevalenza:
  - Scandinavia, Cina, Giappone, India
  - Uomini/Donne = 1.8/1 – 1/1

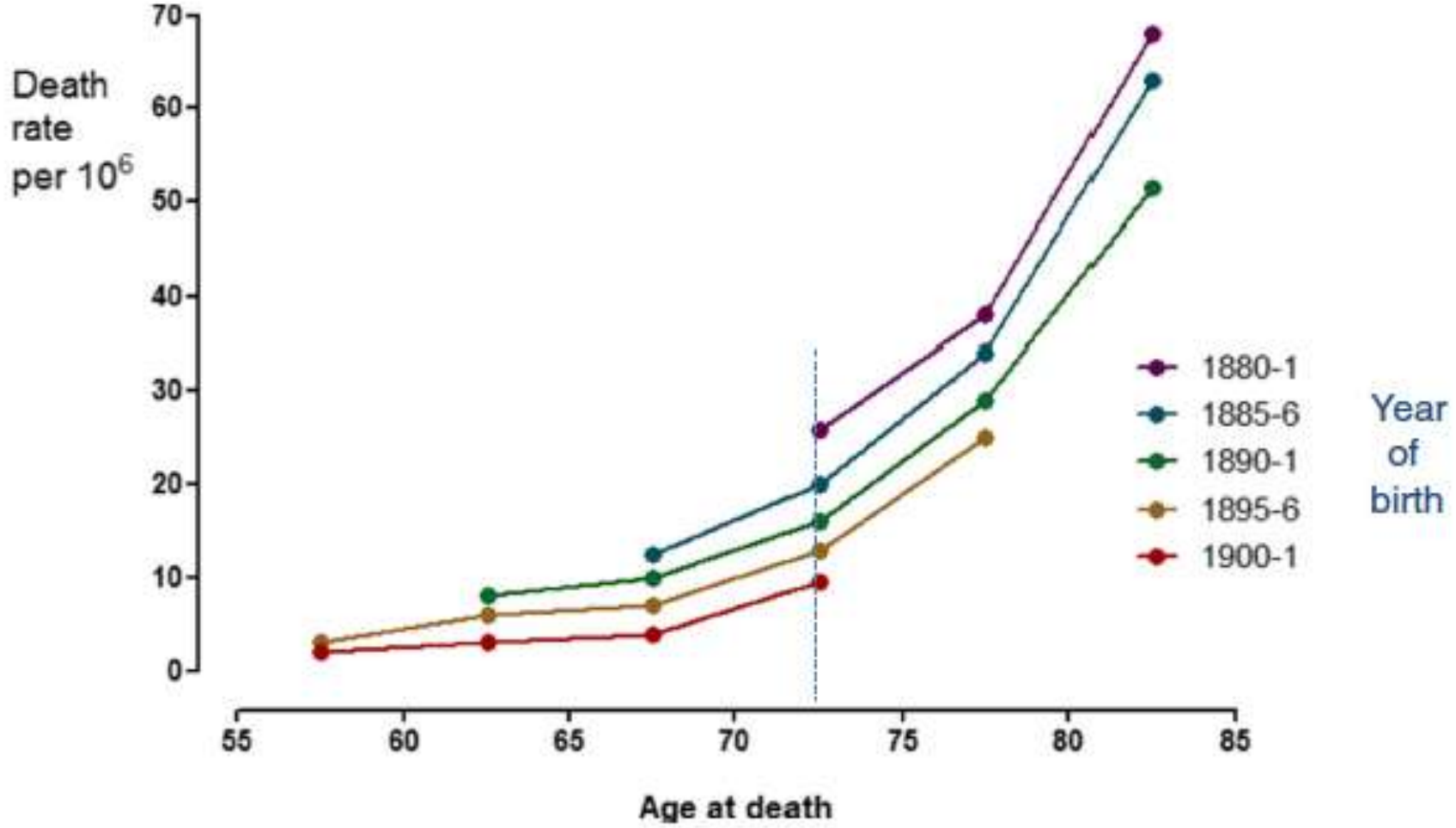


Fig. 2 – Proportion of death certificates issued in England & Wales that mentioned Paget's disease in successive cohorts born between 1880 and 01 and 1890–01. Note that at an age of death of 72½ (dotted line) the proportion had fallen from 25% to 9%. Data adapted from Gardner & Barker [17].

PAGET DISEASE IN ITALY

- Prevalence:
  - approximately 1 % (0.7→2.4% age)
  - higher in males
- Secular Trends:
  - no apparent decrese in prevalence
  - probable decrease in clinical severity
- Familial Aggregation:
  - 15-28 % (SQSTM1 mutation in 5-10%)
  - probably understimated
- Environment:
  - more prevalent in rural vs. urban areas
  - association with animal-related factors
- Regional Clustering:
  - high prevalence areas detected in Toscana, Calabria and Campania
  - increased clinical severity in Campania region

Gennari L et al. J Bone Miner Res. 2005; 20: 1845-50.

METABOLISM CLINICAL AND EXPERIMENTAL 80 (2018) 5–14

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Paget's disease of bone

*Tim Cundy**

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La scoperta più significativa è stata che circa il 30% del PDB familiare è associato a mutazioni ereditarie dominanti nel gene SQSTM1.

Rispetto agli individui affetti senza mutazioni, **quelli con mutazioni SQSTM1 tendono ad avere un fenotipo più grave**, presentandosi in **età precoce** e con una malattia **più estesa**.

Sono state associate circa 30 diverse mutazioni in SQSTM1 a PDB, ma una, p.**P392L**, è di gran lunga la più comune ed è stata trovata in popolazioni di tutto il mondo.

Nelle ultime generazioni di pz affetti da PDB il **fenotipo è attenuato e/o ritardato** e l'entità del coinvolgimento scheletrico risulta inferiore

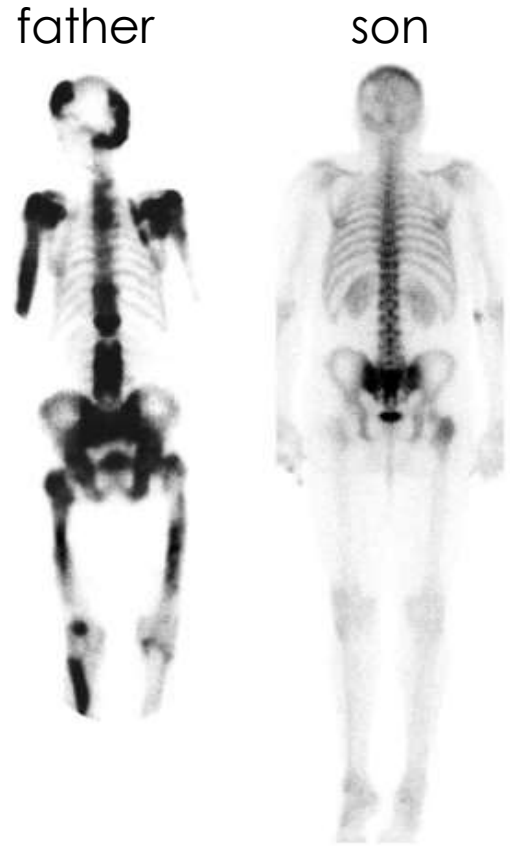

Fig. 3 – Bone scintiscans from a father and son who both carry a truncating mutation in *SQSTM1*. The father had severe symptomatic polyostotic disease when he was diagnosed at the age of 39 - his ALP was 1200 u/L. His son was asymptomatic when diagnosed with monostotic PDB of the sacrum at the age of 44 - his ALP was 81 u/L (normal < 120 u/L).

Loci di suscettibilità per m. di Paget

il Pdb2 viene oggi associato alla sindrome dell'osteolisi espansile familiare (Feo), al Paget giovanile e all'iperfosfatasia scheletrica espansile (Esh) e a rari disordini scheletrici su base familiare.

Locus	Cromosoma	Gene/i	Commenti
Pdb1	6p21.3	Hla	Probabile falso positivo
Pdb2	18q21.1-22	Rank	Osteodistrofia di Paget (forme rare e gravi)
Pdb3	5q35	SQSTM1*	Il più importante gene legato all'osteodistrofia di Paget
Pdb4	5q31	-	
Pdb5	2q36	-	
Pdb6	10p13	-	
Pdb7	18q23	-	Potrebbe essere un falso positivo. Molti membri familiari che mostrano *linkage* con il Pdb7 ora mostrano mutazioni a livello del gene Sqstm1

*SQSTM1= Sequestosoma 1

PROTEINOPATIA MULTISISTEMICA e MALATTIA DI PAGET

I tessuti interessati dal PDB hanno in comune inclusioni ubiquitina positiva che contengono proteine leganti l'RNA come TDP- 43, hnRNPA1 e hnRNPA2B1, ma possono anche contenere **proteine che mediano l'autofagia dipendente dall'ubiquitina** come **p62, VCP e optineurina** Ad oggi le mutazioni in cinque geni sono state associate a proteinopatia multisistemica: **VCP, HNRNPA2B1, HNRNPA1, SQSTM1** e MATR3. La malattia di Paget è stato associato a tutti questi tranne l'ultimo.

PDB associato a proteinopatia multisistemica si verifica in un'età più giovane rispetto al classico PDB e può a volte essere la sua caratteristica di presentazione. I geni implicati nella proteinopatia multisistemica codificano per proteine leganti l'RNA o proteine che mediano l'autofagia ubiquitina-dipendente. Il risultato sembra essere eccesso di assemblaggio di granuli di RNA (che normalmente controllano la post-trascrizione metabolismo dell'mRNA) accoppiato con il fallimento di degradazione autofagica. Un piccolo studio ha riferito che particolari alleli in alcuni geni correlati all'autofagia sono anche associato al rischio di PDB [1].

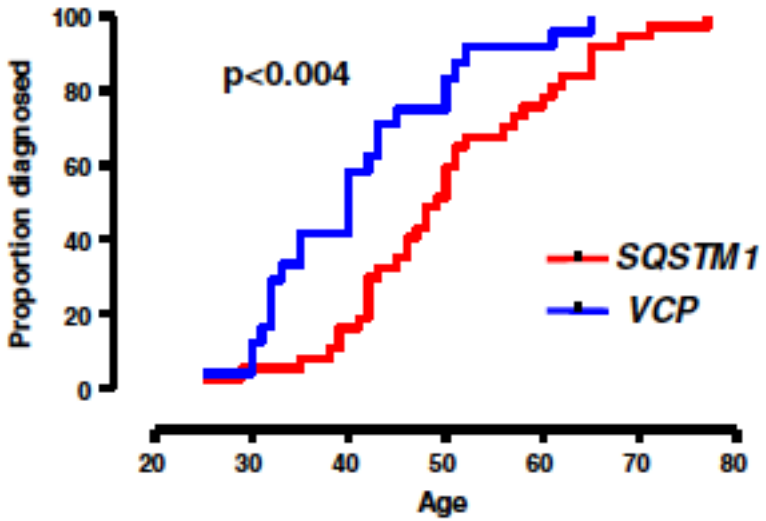

Fig. 4 – Age at diagnosis of Paget's disease in 24 patients with multisystem proteinopathy due to VCP mutations (from Kimonis et al. [46]) and 37 patients with SQSTM1 mutations but no multisystem proteinopathy (data from Auckland, New Zealand). Paget's disease was diagnosed about 10 years earlier in VCP mutation carriers.


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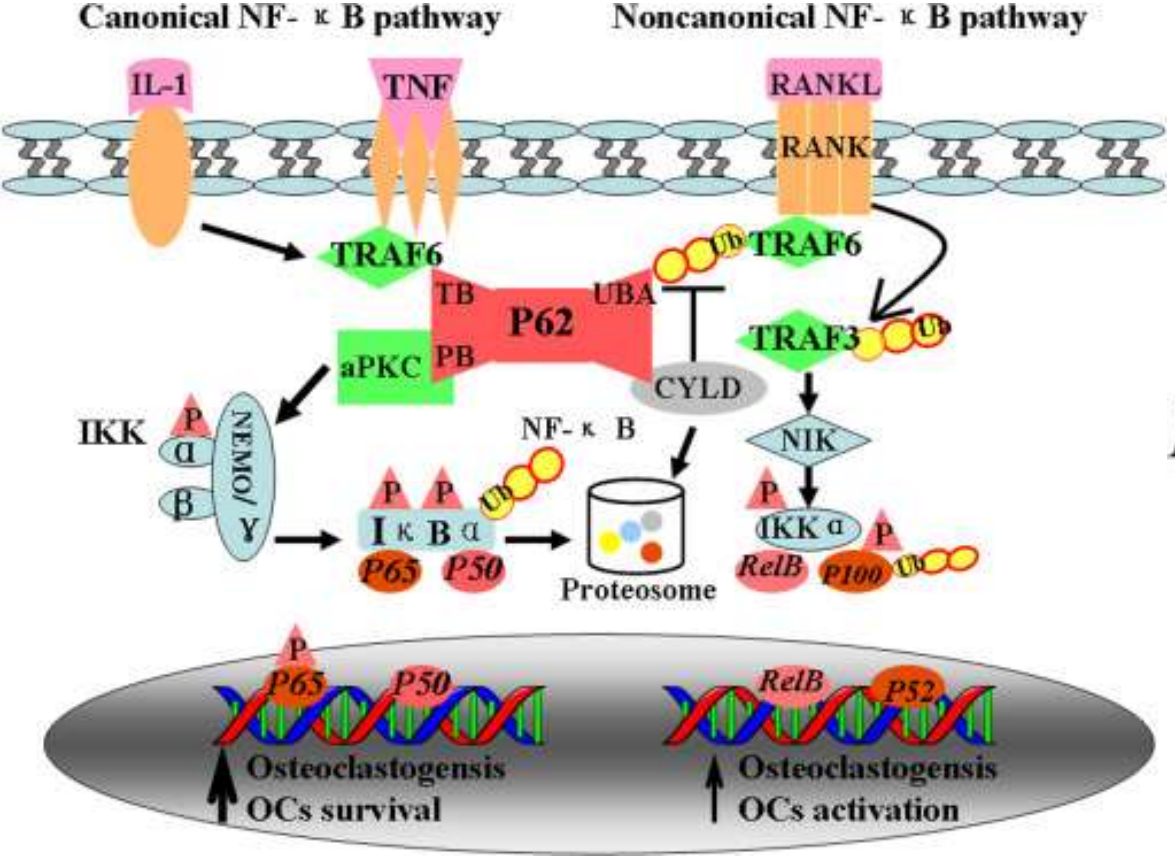
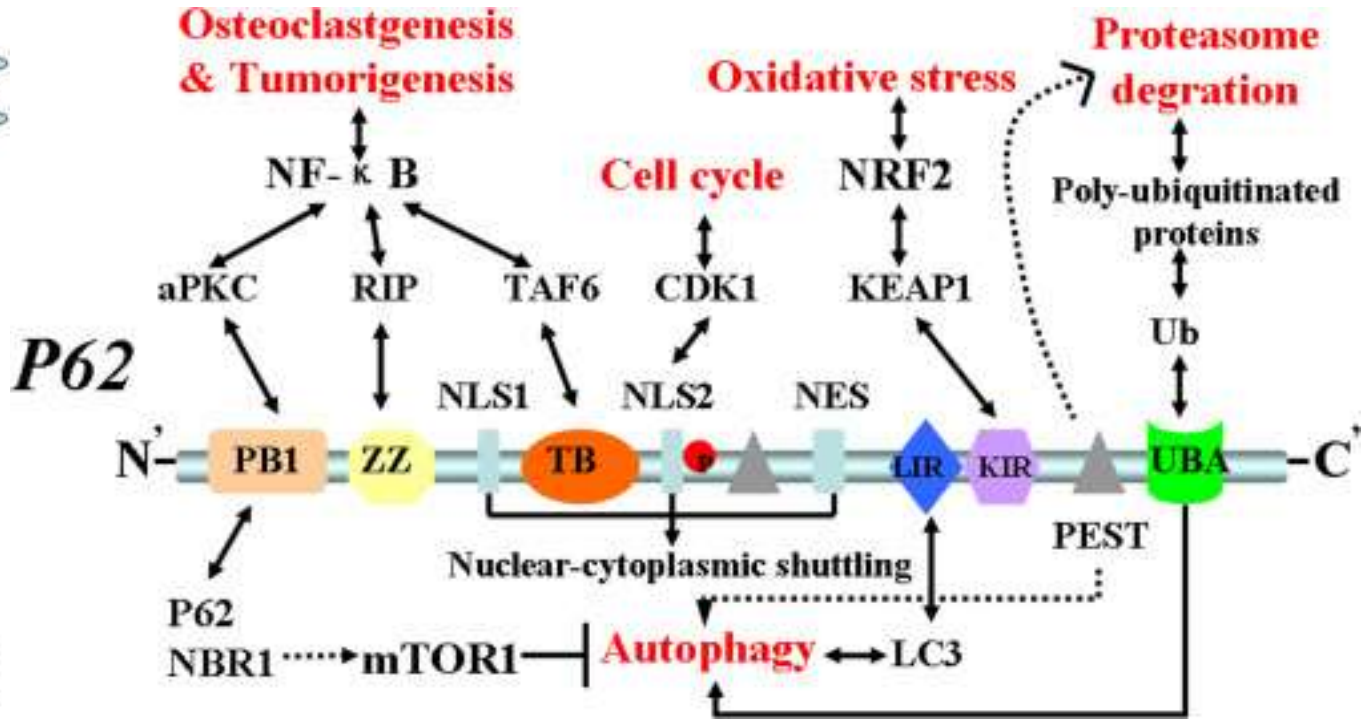
Paget's disease of bone

*Tim Cundy**

Department of Medicine, Faculty of Medical & Health Sciences, University of Auckland, New Zealand

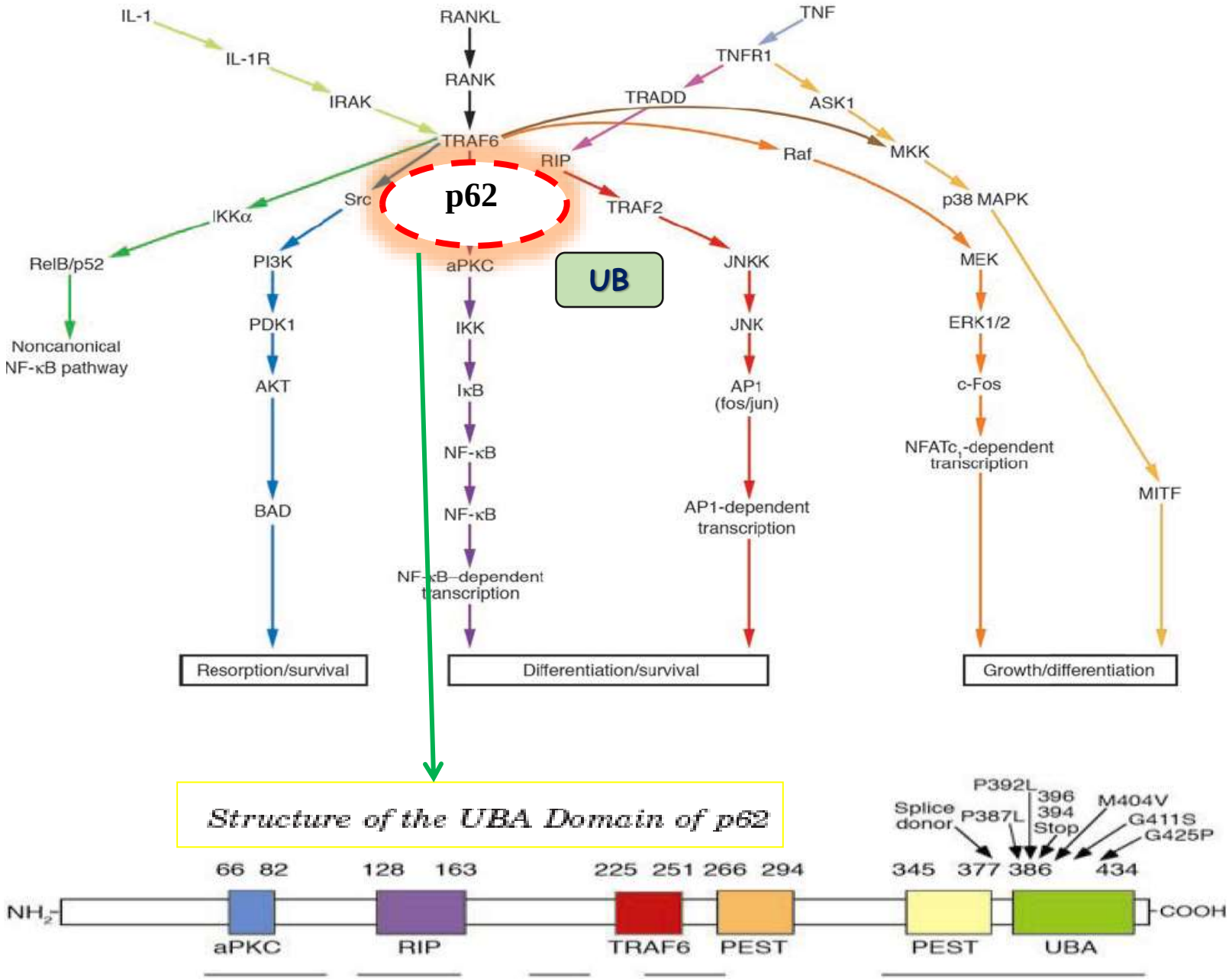
1.Usategui-Martín R et al. PLoS ONE 2015;10(6):e0128984.





SQSTM1 codifica per l'onnipresente ***proteina dello scaffold*** intracellulare multidominio, **p62,** coinvolta in varie vie di segnalazione. Il modo in cui i cambiamenti in p62 predispongono al PDB non è completamente compreso. La proteina ha una serie di **funzioni**, ma la maggior parte dell'attenzione è stata concentrata su quelle che influenzano la **differenziazione, l'attività e la sopravvivenza** degli **osteoclasti**.
Questi includono la trasduzione dell'**NFKB e le vie Keap1 / Nrf2** indotte dallo **stress ossidativo**, che prendono di mira le proteine per la degradazione e la formazione dell'**autofagosoma e l'apoptosi**.
p62 è coinvolto in molte vie di segnalazione degli osteoclasti attivate da RANKL. **L'autofagia è un percorso critico per la rimozione di proteine e organelli danneggiati e inclini all'aggregazione**. p62 è un recettore del carico per l'autofagia mediata dall'ubiquitina.

Effetto delle mutazioni del gene del sequestosoma 1 (SQSTM1)



Sono state descritte 11 differenti mutazioni tutte presenti nel dominio legante l'ubiquitina (UBA domain).

Viene danneggiata la capacità della proteina p62 di veicolare le proteine legate all'ubiquitina all'interno della via NF-kB per essere degradate, mentre resta intatta la funzione "scaffold". Questo potrebbe provocare una **prolungata attivazione della via NF-kB e quindi un'aumentata osteoclasto-genesi.**

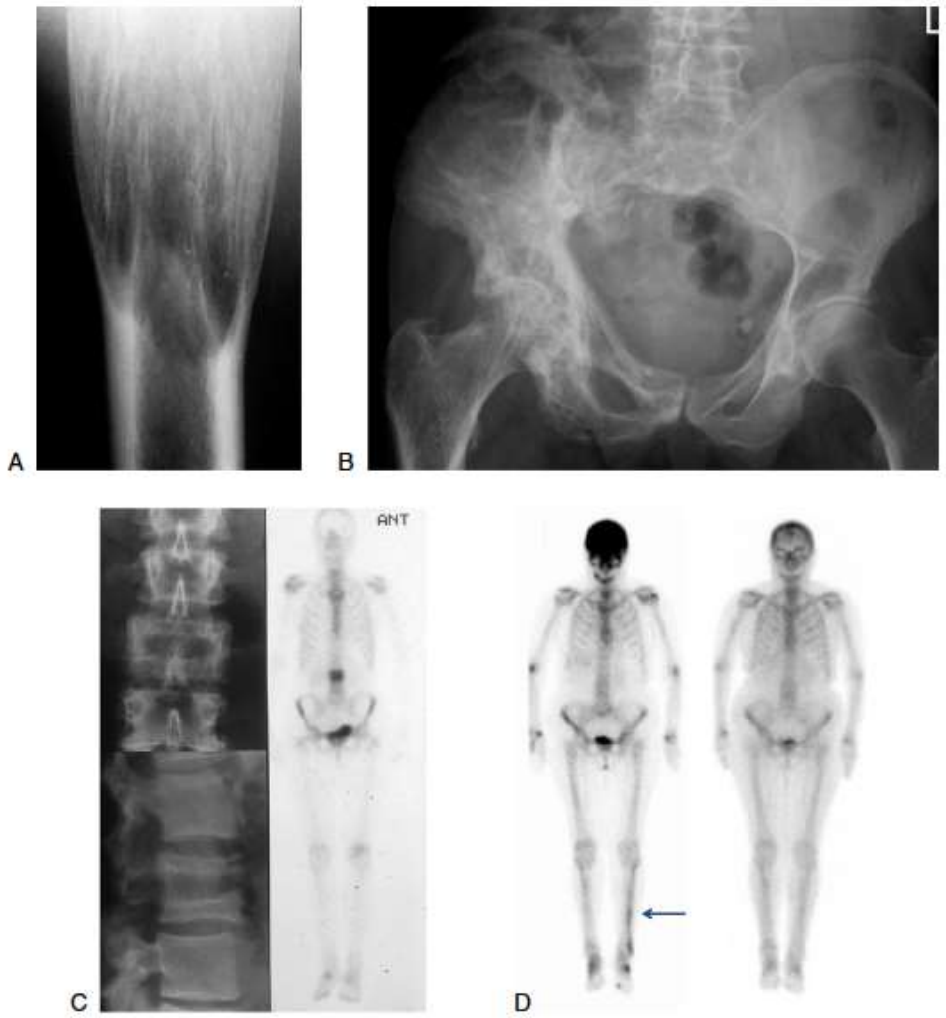
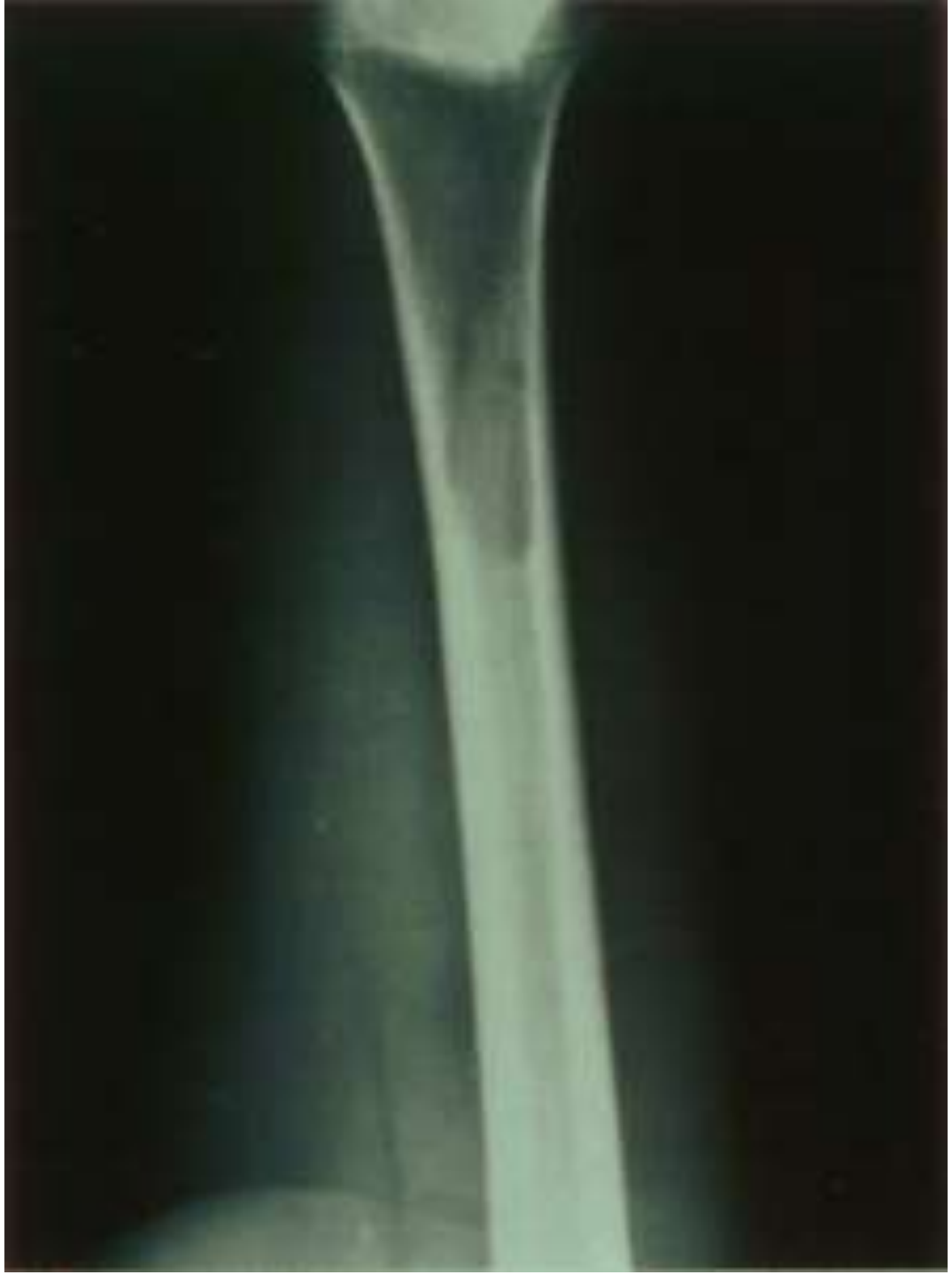
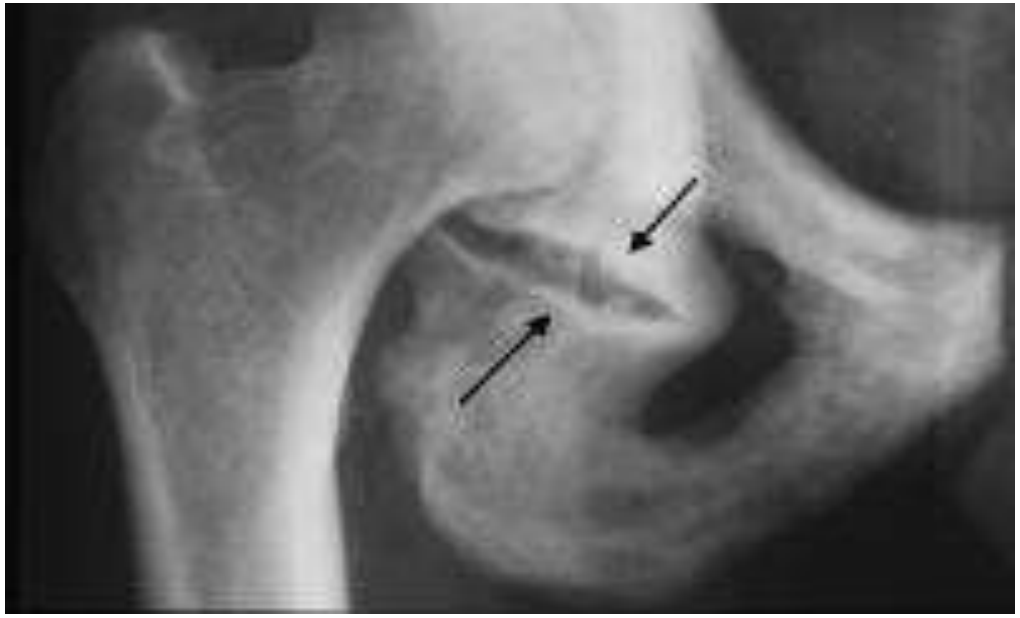


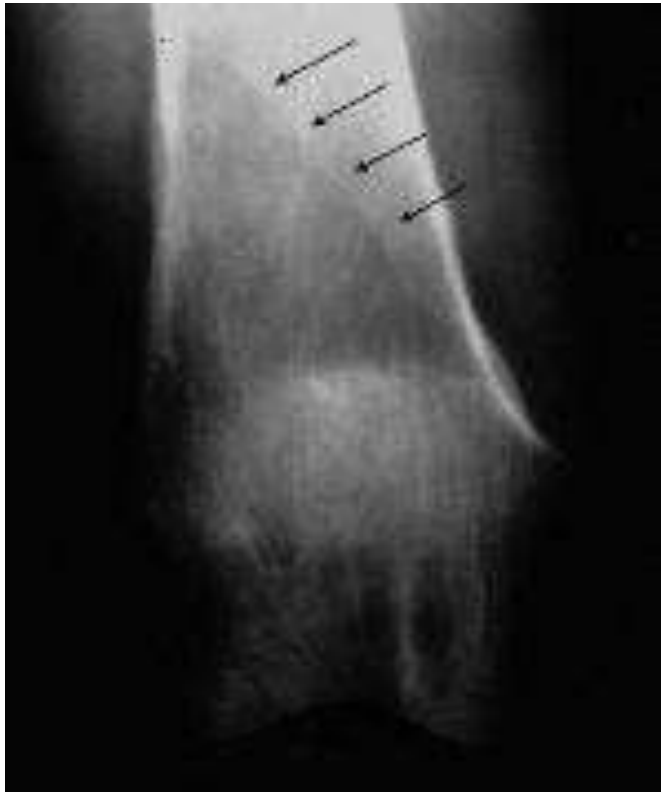
Fig. 1 – A A 'lytic wedge' of osteoclast-led resorption in the tibia. Note the thin cortex which makes this phase vulnerable to fracture. B Paget's disease affecting the right femur and right hemipelvis causing secondary osteoarthritis at the hip joint and acetabular protrusion. C Monostotic Paget's disease affecting the third lumbar vertebra. Note that the bone is enlarged. D An 85 year old woman with PDB affecting the skull and left fibula (arrowed) before (left) and after a 6 month course of oral alendronate (40 mg/day). Note the marked reduction in isotope uptake.

Table 1 – Radiographic features of Paget's disease.

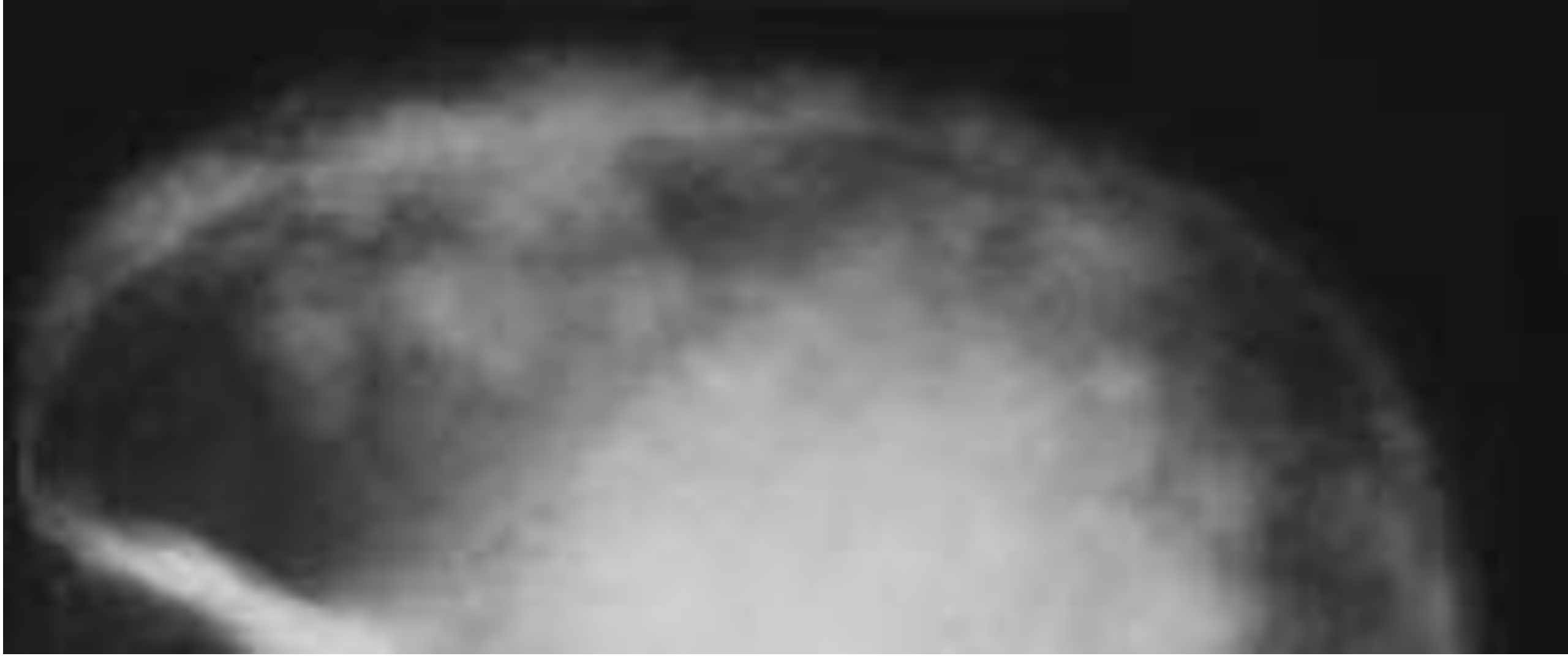
- Classical triad
  - Thickening of the cortex
  - Accentuation of the trabecular pattern
  - Increased size of bone
- Cyst-like areas
- Skull involvement
  - Inner and outer table involved
  - Diploic widening
  - Osteoporosis circumscripta - well-defined lytic lesion in skull
  - "Cotton wool" appearance of thickened calvarium
  - Basilar invagination with encroachment on foramen magnum
  - Sclerosis of skull base
- Long bones
  - V-shaped defect of advancing lytic tip in diaphysis
  - Lateral curvature of femur
  - Anterior curvature of tibia
  - Fissure fractures
- Pelvis
  - Thickened trabeculae in sacrum, ilium
  - Rarefaction in central portion of ilium (looks like a large lytic lesion)
  - Thickening of iliopectineal line
  - Acetabular protrusion with secondary degenerative joint disease
- Spine
  - Coarse trabeculations at periphery of bone
  - "Picture-frame vertebra"
  - Enlarged vertebral body; reinforced peripheral trabeculae/lucent center
  - "Ivory vertebra" with increased density
  - "Mickey Mouse" appearance on scintiscan







Hot phases



Mixed phase: presence of osteolytic and disorganized osteoblastic activity. "Cotton wool" aspect of the affected bones

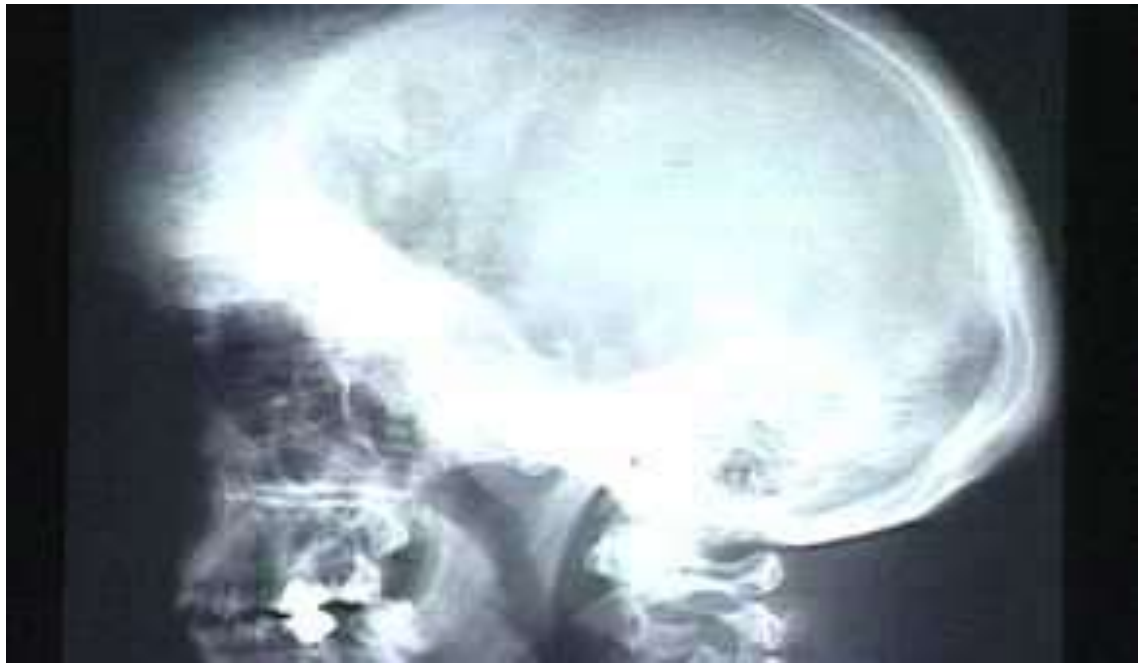
Table 1 Clinical Manifestations and Complications of Paget's Disease of Bone

Musculoskeletal	
Bone pain, bowing of long bones, enlarged skull, osteoarthritis of joints adjacent to pagetic lesions, bone fractures, sarcoma (osteosarcoma, chondrosarcoma, fibrosarcoma), giant cell tumors	
Neurologic	
Hearing loss, platybasia, spinal stenosis, vascular steal syndromes, increased cerebral spinal fluid pressure, cranial nerve deficits (rare)	
Cardiovascular	
High-output heart failure, aortic stenosis, endocardial calcifications	
Genitourinary	
Nephrolithiasis	
Metabolic	
Hypercalcemia (in some patients), immobilization hypercalciuria, hyperuricemia	

Based on information from Ralston SH. Paget's disease of bone. *N Engl J Med*. 2013;368:644-650 and Whyte MP. Paget's disease of bone. N Engl J Med. 2006;355:593-600.

Complications of Paget's Disease

Malattia ossea di Paget



Complications of Paget's Disease

- Reduced quality of life
- Improved mortality (R.R. 1.3 after 5 years of disease)
- Importance of early diagnosis and treatment to prevent onset and development of complications

Table II - Indications for treatment of Paget disease of bone.

Pain in pagetic bones
Neurological complications
Significant osteolytic lesions
Involvement of long bones, vertebrae or base of skull
Before surgery involving pagetic bones
Significant joint involvement (e.g. hip joint)

Bertoldi et al. Reumatismo 2014 66 (2): 171-183

Neoplastic complication of Paget's disease

- Sarcoma (< 1%)
  - osteosarcoma
  - chondrosarcoma
  - fibrosarcoma
- Giant-cell tumor (rarely malignant)

High-risk sites for malignant transformation

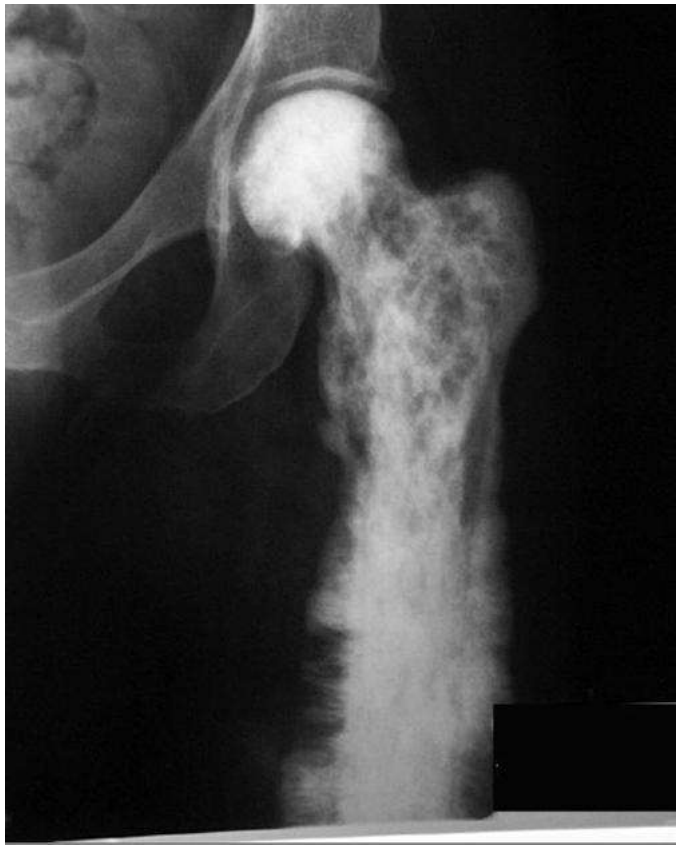
- **Extremities**
- **Pelvis.**

Sarcomatous transformation should be suspected

- sudden onset of pain,
- rapid worsening of previous pain

- increased deformity
- rapid increase in the serum ALP levels

Osteosarcoma in m. di Paget



JOURNAL OF BONE AND MINERAL RESEARCH
Volume 21, Supplement 2, 2006
Online reference number: doi: 10.1359/JBMR.06S211

Osteosarcoma in Paget's Disease of Bone

Marc F Hansen,[1] Margaret Seton,[2] and Anand Merchant[1]

ABSTRACT: Paget's disease of bone (PDB) is a focal disorder of bone metabolism first described by Sir James Paget in 1876. It is presumed benign in nature and mediated by abnormal osteoclast function. The incidence of osteosarcomas complicating PDB is estimated at <1%. These cancers occur mostly in persons with long-standing, polyostotic disease and affect patients in their seventh decade or when osteosarcoma is remarkably rare in the general population. Epidemiological studies suggest that this late peak of osteosarcomas is absent in regions where Paget's is infrequently reported. Whereas PDB has a predilection for the axial skeleton, skull, femurs, and tibias, pagetic osteosarcoma tend to spare the spine, and are reported more commonly in the pelvis, femur, humerus, and skull. A molecular basis for the association of osteosarcoma with Paget's disease is unclear. These osteosarcomas are osteogenic in origin, consistently arise in sites of pagetic bone, and may present as metachronous, multifocal lesions. On histopathology, the lesions are usually osteoblastic, and the tumor phenotype is sometimes characterized as an exaggerated, chaotic form of the accelerated bone remodeling that characterizes PDB. New insights from the biology of adolescent osteosarcomas, *VCP* and *SQSTM1* mutations now defined in patients with Paget's disease, and emerging evidence that stromal lesions are present in patients with Paget's disease are changing the way we think about the pathogenesis of PDB and the rare complication of pagetic osteosarcomas.
J Bone Miner Res 2007;21:P58–P63. Online reference number: doi: 10.1359/JBMR.06S211

Key words: Paget's disease of bone, osteosarcoma, bone remodeling, genetics

TABLE 1. ANATOMIC DISTRIBUTION OF PAGETIC AND ADOLESCENT OSTEOSARCOMA[46]

Anatomic site	*Adolescent osteosarcoma*	*Pagetic osteosarcoma*
Skull	2%	8%
Mandible	3%	2%
Humerus	9%	19%
Femur	47%	24%
Proximal tibia	15%	10%
Ilium	7%	26%
Sacrum	<1%	3%
Ribs	<1%	3%
Vertebrae	<1%	3%

PAGETIC OSTEOSARCOMA REPRESENTS A DIVERSION FROM THE NORMAL COURSE OF PAGET'S DISEASE

Am J Hum Genet. 2016 Feb 4; 98(2): 275–286.
Published online 2016 Feb 4. doi: 10.1016/j.ajhg.2015.12.016
PMCID: PMC4746367

ZNF687 Mutations in Severe Paget Disease of Bone Associated with Giant Cell Tumor

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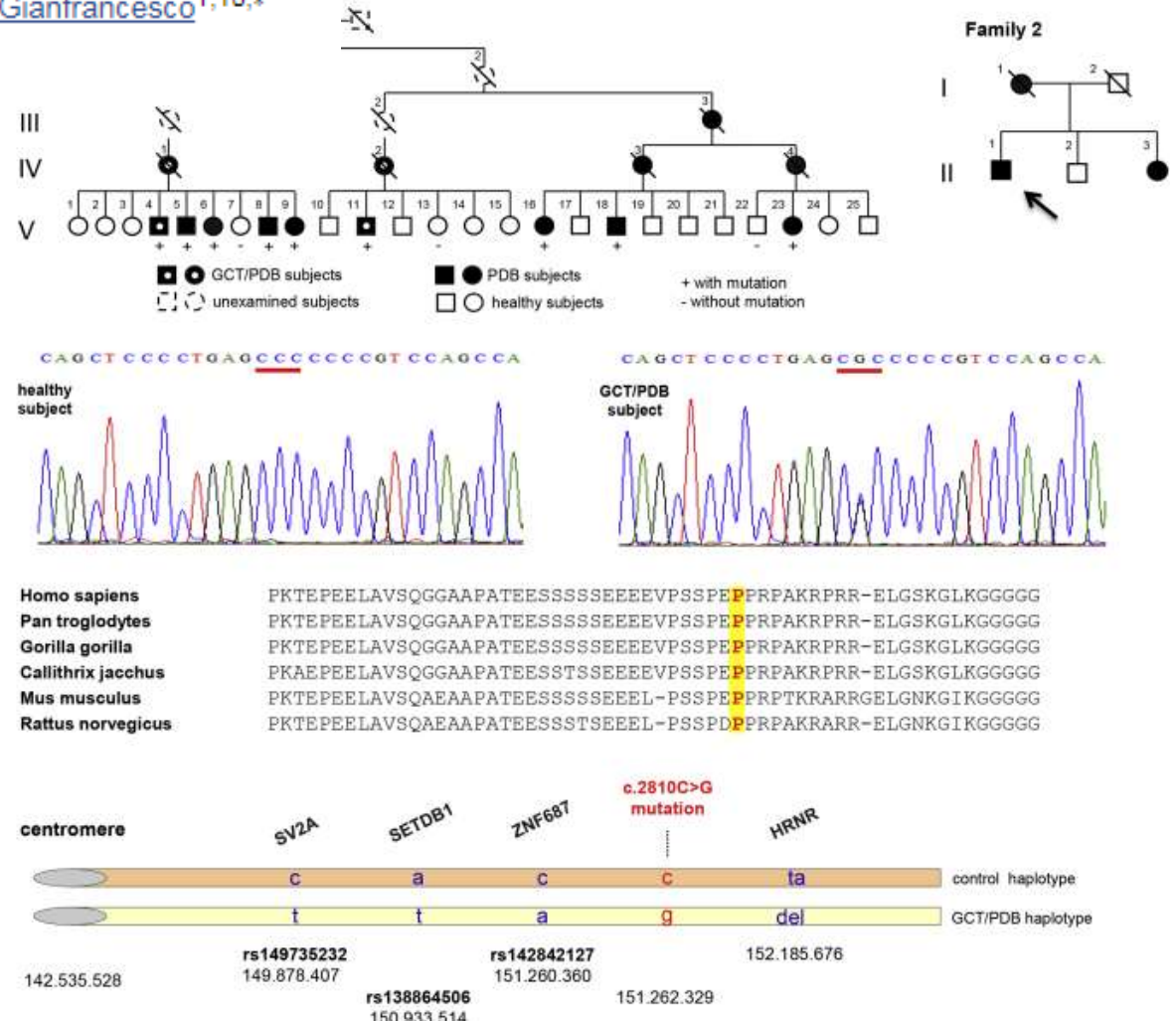
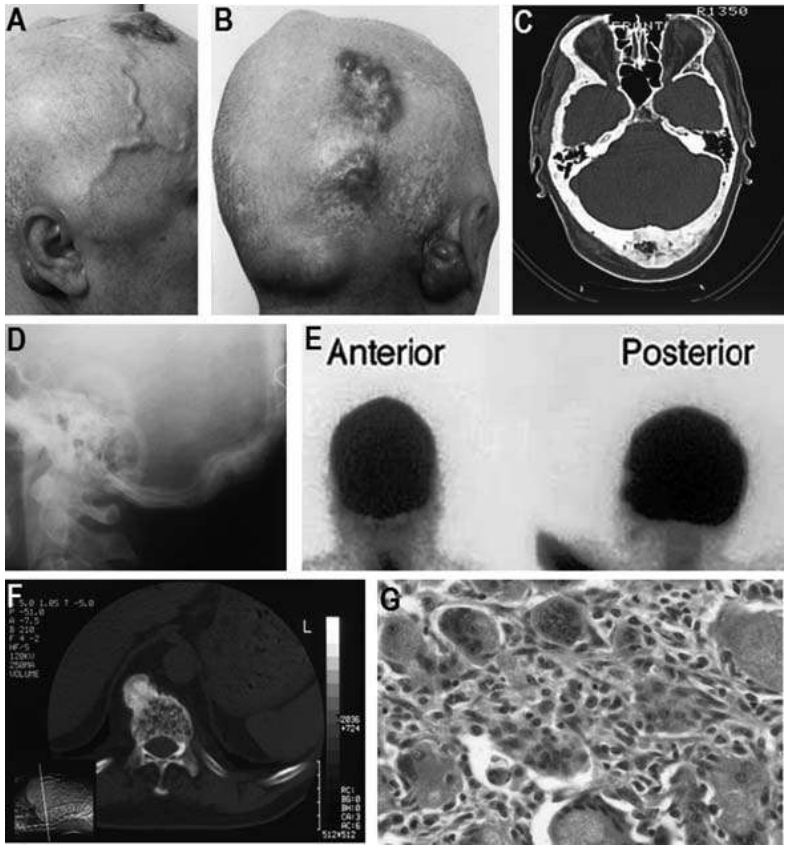
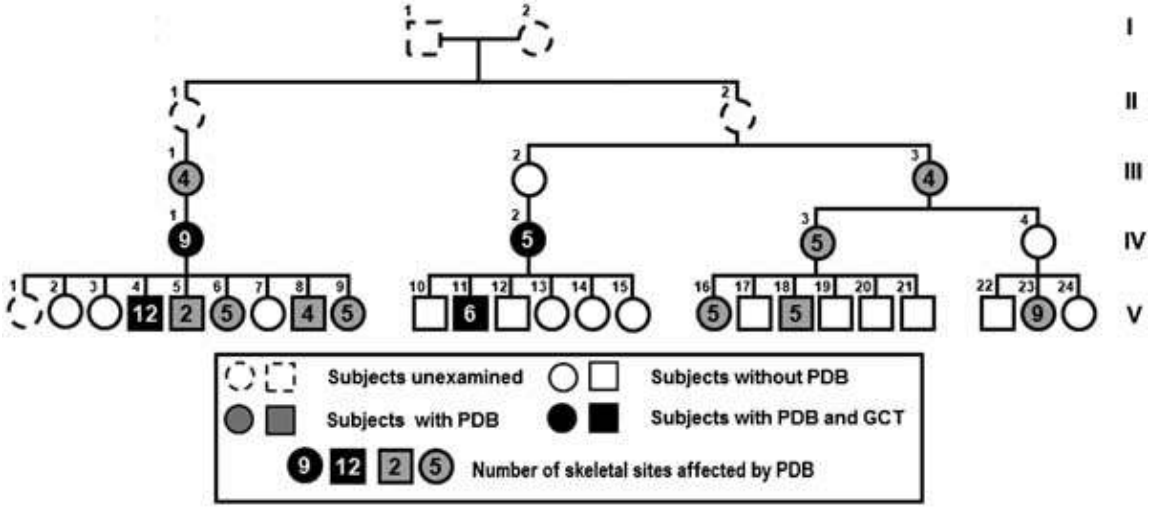
ZNF687 (indicato come gene bersaglio del fattore di trascrizione NFkB) è fortemente espresso durante l'osteoclastogenesi e osteoblastogenesi ed è drammativamente **sovraregolato nel tessuto tumorale degli individui con GCT**. Inoltre è sovraregolato nel sangue periferico anche in quei soggetti con la mutazione SQSTM1.



Giant cell tumor occurring in familial Paget's disease of bone: Report of clinical characteristics and linkage analysis of a large pedigree





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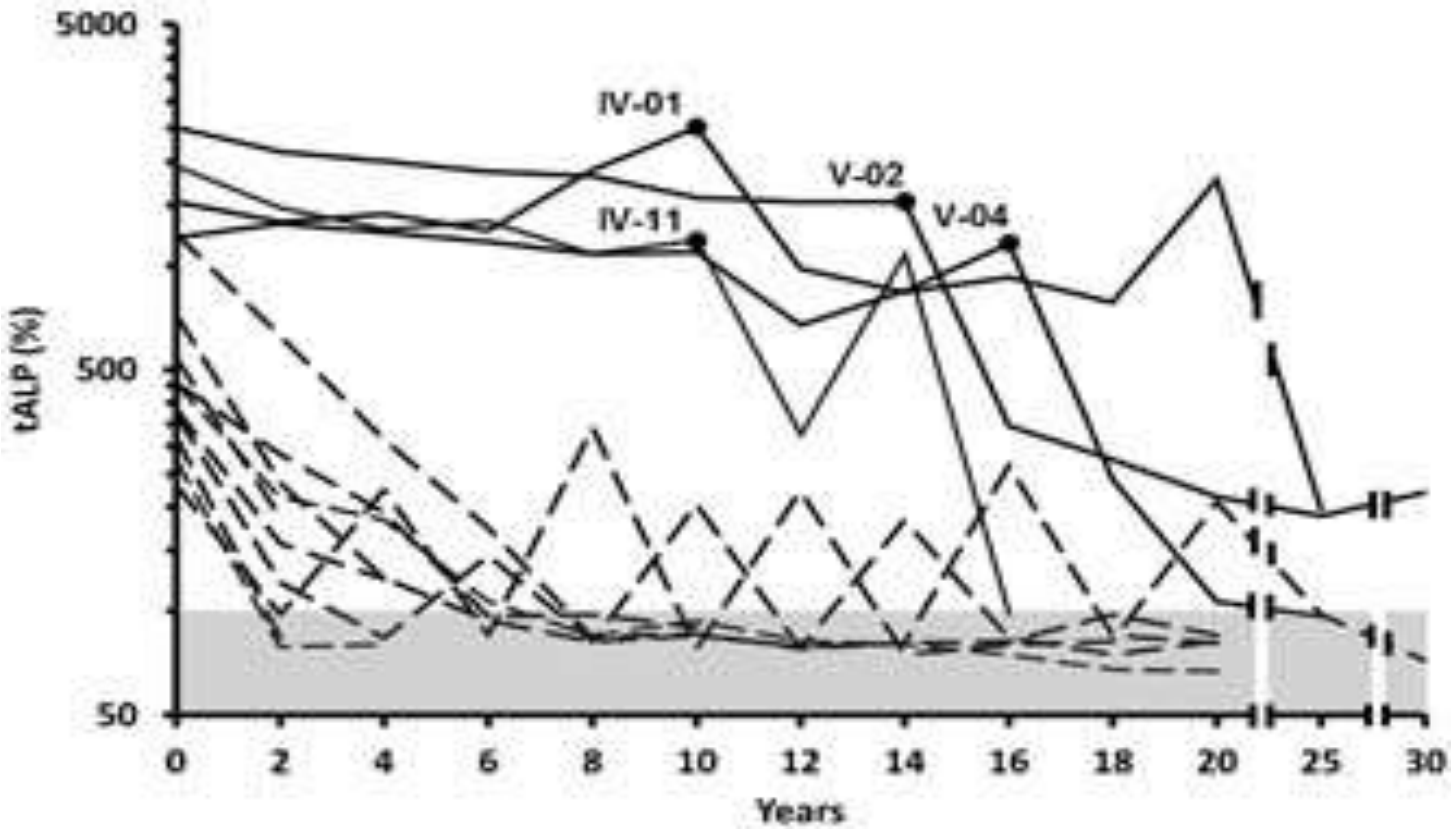

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Schemi terapeutici dei BP nella MdP

Bisfosfonato	Dose e Posologia	Indicazione approvata	Note
Etidronato	2.5-20mg/Kg/die max 400mg/die per 6 mesi	SI	Solo in pz. con malattia a modesta attività (ALP< 2 v.n.)
Clodronato	os: 800 mg/die/6 mesi os: 1600 mg/die/3 mesi ev: 300 mg/die x 5 gg	NO	
Tiludronato	os: 400 mg/die/6 mesi	NO	Non disponibile in Italia
Pamidronato	ev: 60- mg ogni 2 settimane x 3	NO	
Neridronato	ev: 200 mg, dose in 1 o 2 giorni	SI	
Alendronato	os: 40 mg/die/6 mesi	NO	
Risedronato	os: 30 mg/die/3 mesi	SI	Non a carico del SSN
Ibandronato	ev: 2-6 mg, dose unica	NO	
Zoledronato	ev: 5 mg, dose unica	SI	

Table III - Management of Paget disease.

Presentation	**Bone pain or deformities**	**↑ALP**	**Rx alterations**
First level exams	**Plain radiography**	**Scintigraphy**	
	if Paget	*if positive*	
	Scintigraphy ALP	Plain radiography of affected bone	ALP
	Uncertain Rx		
Second level exams	MRI - CT - Others		
	Uncertain diagnosis		
Third level exams	Bone biopsy		
Treatment	*If active disease*		
	Bisphosphonate		
Follow-up	ALP assessment after 6 month		
	↓≥25%		↓<25%
	Relapse: ↑ALP ≥25% of normal value (upper limit) or Reduction ALP <50%		
	Re-treatment Higher dosage of Bps other Bps		

ALP, alkaline phosphatase; Rx, x-ray; MRI, magnetic resonance imaging; CT, computed tomography; Bps, bisphosphonates.

Bertoldi et al. Reumatismo 2014 66 (2): 171-183

REVIEW

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Paget's Disease of Bone: Diagnosis and Treatment

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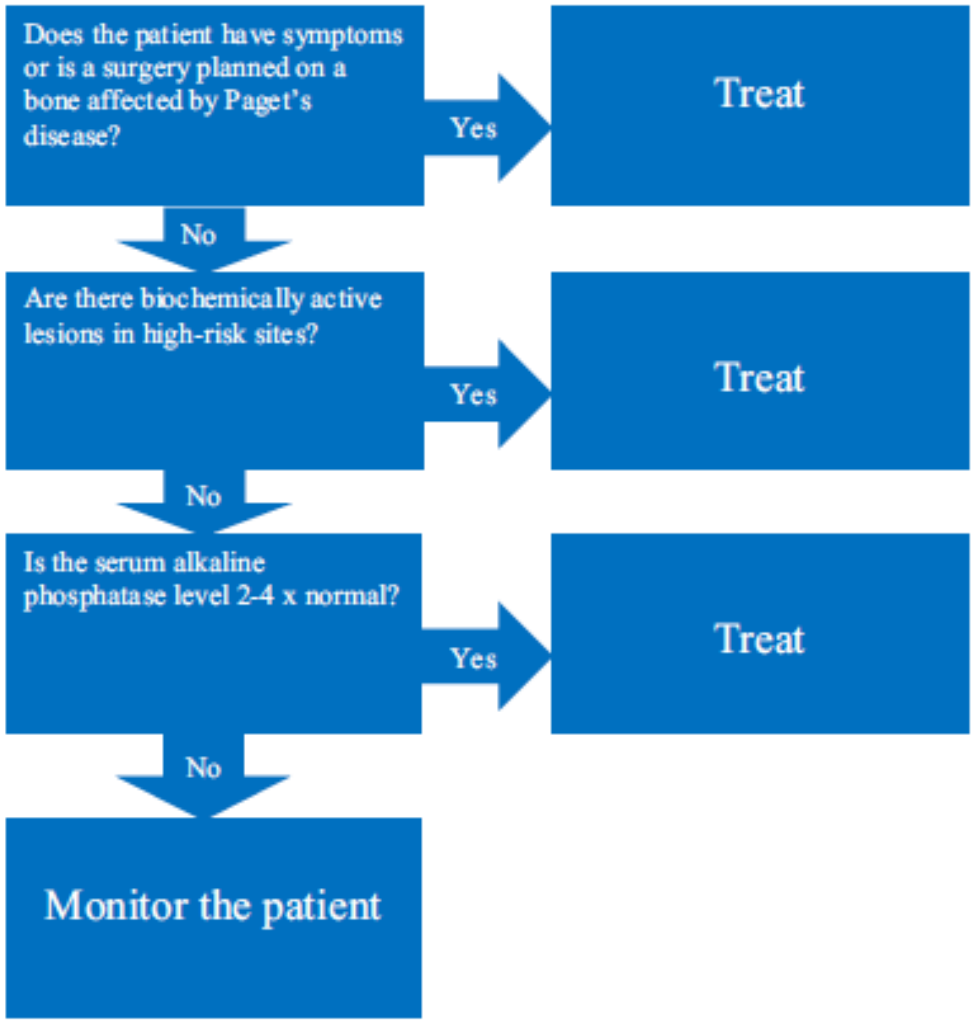
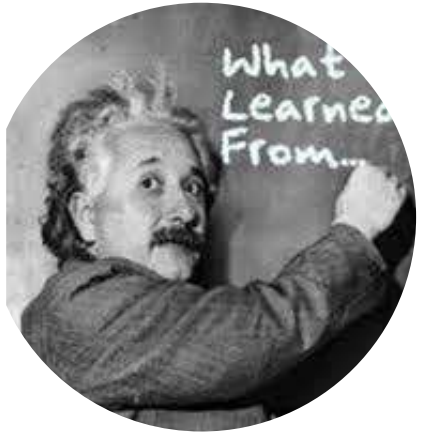
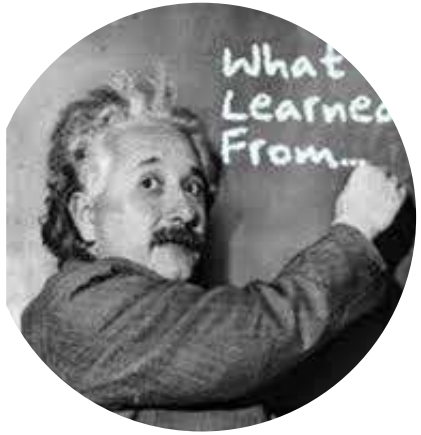




CONCLUSIONI

- Predisposizione genetica, fattori ambientali, infezioni virali
- Spesso asintomatica e non diagnosticata nelle fasi precoci
- Complicanze→Osteosarcoma
- ALP totale è il marker di turnover osseo più utilizzato nella pratica clinica (ALP ossea in epatopatie e nelle forme monostotiche)



CONCLUSIONI

- Scintigrafia ossea di follow up quasi mai giustificata (solo nelle forme monostotiche)
- Il Nadir dopo trattamento con BP è a distanza di 6 mesi
- Riattivazione in caso di ALP > 25%
- Resistenza al trattamento se la riduzione di ALP è < 50% dai valori basali

APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

8a edizione

REUMATOLOGIA E RIABILITAZIONE

Torino, 15 e 16 ottobre 2021

Responsabili scientifici

Enrico Fusaro

Giuseppe Massazza

SAVE THE DATE